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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,729	12/06/2004	Berislav V. Zlokovic	GRT/4061-28	9946

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,729	ZLOKOVIC, BERISLAV V.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *7-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6/04,8/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 9 January 2007 have been entered. Claims 1 – 26 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group 1, (claims 1 – 6) in the reply filed on 9 January 2007 is acknowledged. The traversal is on the ground(s) that examination of claims 7 – 26 along with claims 1 – 6 would not constitute a serious burden. This is not found persuasive because the different groups of claims are drawn to different methods which require different starting materials and for which divergent searches are required. Consideration of claims 7 – 12 requires search for methods of administering drugs as well as search for the drugs of undefined structure. This would require searching the prior art for all drugs which have the effect, and then determining whether those drugs had ever been administered to the appropriate patients. Such search is not required for the methods of assaying vascular dysfunction of Group 1. Further, methods of screening drugs (claims 13 – 18) require search for the steps of assaying for vascular dysfunction not caused by amyloid, which is not required for consideration of Group 1. The remaining groups also require different steps or compounds which are not required for consideration of Group 1. Thus contrary to applicant's assertions, consideration of the additional five groups would in fact constitute a serious burden for the examiner. It is noted that applicant did not traverse the examiner's determination that lack of unity of invention exists in the instant application.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 7 – 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9 January 2007.

4. Claims 1 – 6 are under examination.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 – 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Shi (1996. J. Clin. Invest. 98:1979 – 1990).

Shi teaches methods of determining whether there is inappropriate senescence in at least the endothelium of subjects, thereby anticipating claim 1. Shi studied several types of subjects, including those with Alzheimer's disease, with AIDS, and normal controls. See Shi, Table 1 on p. 1985 for a description of the subjects and which conditions they had. The reference by Shi therefore anticipates claims 1 and 2, since the subjects studied had Alzheimer's disease. Note that the breadth of claim 1 does not require that patients with any particular disorder have either increased or decreased senescence, it merely requires "determining". Shi used the TUNEL method to study apoptosis, which is quite reasonably a form of "determining" (see Shi, p. 1980 column 2 for description of the TUNEL assay). The subjects were human, anticipating claim 3; see p. 1980 "Brain tissue" for description of how brains were obtained from hospitals, and Table 1 which clearly indicates that the patients were human, note they had diseases which only occur in humans, such as AIDS. Furthermore, the TUNEL method reveals whether or not cells have undergone, or are about to undergo, apoptosis. Note that the last column of Table 1 clearly indicates that many patients showed apoptosis in endothelial cells, thereby anticipating claim 5.

6. Claims 1 – 3 and 6 rejected under 35 U.S.C. 102(b) as being anticipated by Partanen (1999. Cancer 86:2406-2412) as evidenced by Cassel et al. (2001. Demography and Epidemiology of Age-Associated Neuronal Impairment. In: Functional Neurobiology of Aging, pp. 31 – 50).

Partanen teaches determining whether there is defective angiogenesis in endothelium. The article describes the results of experiments in which VEGFR-3 protein was measured in various tumors. Partanen particularly teaches determining whether there is defective angiogenesis by correlating the presence of VEGFR-3 to the presence of newly-formed blood vessels. See particularly p. 2411, first and second paragraph, where the authors conclude that VEGFR-3 is widely found in proliferating blood vessels. As the entire article is on point to analysis of cancerous tumors, and the tumors have excessive (i.e. defective) angiogenesis, the reference fairly teaches all the steps of claim 1. Note that the breadth of claim 1 does not require that patients with any particular disorder have either increased or decreased senescence, it merely requires "determining". Claims 1 and 2 both encompass patients "at risk for" Alzheimer's disease, and Cassel teaches that all patients are in fact at risk for Alzheimer's.

See particularly Cassel, end of p. 35 and Figure 4.3 on p. 36, which indicate that the risk of Alzheimer's disease increases with age; thus claims read on the population of subjects in general. Claim 3 is anticipated as the tumor samples which comprise endothelium are from humans. Claim 6 is anticipated as the reference by Partanen teaches VEGFR-3 is associated with defective differentiation of endothelial cells, particularly as the cells differentiate into cancerous tissue.

7. Claims 1 – 4 and 6 rejected under 35 U.S.C. 102(b) as being anticipated by Mulliken (1982. Surgery 92(2):348-353) as evidenced by Cassel et al. (2001. Demography and Epidemiology of Age-Associated Neuronal Impairment. In: Functional Neurobiology of Aging, pp. 31 – 50).

As discussed above, Cassel provides evidence that all patients are at risk of Alzheimer's disease. Mulliken teaches taking tissue from hemiangiomas and blood vessel malformations and culturing the tissue in medium. Specifically, at p. 348 Mulliken teaches obtaining the tissue surgically and the methods used to culture it. Endothelial tissue was specifically selected whereas other tissue was discarded. The reference also teaches that hemiangiomas undergo tube-formation in vitro and the authors report this phenomenon is *in vitro* angiogenesis (see for example p. 350, second column). Mulliken also reports that tissue from four malformations, including atrial, venous, and lymphatic, did not show the same outgrowth of tubes when in culture (see p. 351). As hemiangiomas are a type of cancer, the increased degree of angiogenesis that they show is clearly defective. Thus the reference by Mulliken teaches the method of claim 4. As claim 4 is anticipated, the parent claim (claim 1) is necessarily anticipated. Since the subjects that were the source of the tissue were human, and all humans are at risk of Alzheimer's disease, claims 2 and 3 are anticipated as well. Since the tissue from the hemiangiomas is not sufficiently differentiated but rather is still in a rapidly growing state, the prior art reference by Mulliken fairly anticipates claim 6 as well.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
March 21, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER